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### **An evaluation of the potential to improve perinatal outcomes by improving antenatal detection of small for gestational age babies in Scotland: a retrospective population cohort study**

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## RESEARCH ARTICLE

# An evaluation of the potential to improve perinatal outcomes by improving antenatal detection of small for gestational age babies in Scotland: a retrospective population cohort study

[version 1; peer review: 2 approved with reservations]

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## Abstract

**Background:** Small for gestational age (SGA) babies are at high risk of perinatal mortality. We aimed to determine the potential to reduce perinatal mortality by improving antenatal detection of SGA babies in Scotland.

**Methods:** We conducted a retrospective population study of all singleton SGA babies born in the 15 Consultant-led maternity units in Scotland in a 3-month period (1<sup>st</sup> Dec 2014 to 28<sup>th</sup> Feb 2015 inclusive). Demographic and pregnancy outcome data were extracted from Scottish birth records for all pregnancies; case note review was performed for all SGA cases [defined as birthweight less than the 10th centile for their gestational age at delivery as defined by the appropriate sex-specific UK-WHO Child Growth Standards].

**Results:** The SGA rate in Scotland was 5.5% (673/12218; 95% confidence interval [CI] 5.1, 5.9) and 27.6% (186/673; 95% CI 24.3, 31.2) of SGA cases were identified prior to delivery. SGA was associated with 18.2% (12/66; 95% CI [10.1%, 30.0%]) of all perinatal deaths. The majority (10/12, 83.3%) of SGA babies who died had been identified as SGA in the antenatal period. There was no difference in perinatal mortality whether SGA was detected or not (5.4% [10/186; 95% CI 2.8, 10.0] in the SGA detected group vs 0.4% [2/487 [95% CI 0.3, 2.2] in the non-detected group after adjusting for risk factors for SGA, gestation at delivery and birthweight centile (Adjusted odds ratio [AOR] 0.85 [95% CI 0.5, 1.5], p=0.556).

**Conclusions:** Despite only around a quarter of SGA babies being

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identified antenatally, the potential to reduce perinatal mortality in the Scottish population by improving SGA detection is limited. Only a minority of perinatal deaths occurred in SGA babies; and in the majority of these SGA was detected antenatally.

### Keywords

Pregnancy, Small for Gestational Age, Stillbirth, Perinatal Morbidity, Birthweight

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## Abbreviations

AC Abdominal Circumference

BMI Body Mass Index

EFW Estimated Fetal Weight

GROW Gestation Related Optimal Weight

NHS ISD NHS National Services Scotland, Information Services Division

INTERGROWTH-21<sup>st</sup> International Fetal and Newborn Growth Consortium for the 21<sup>st</sup> Century

RCOG Royal College of Obstetricians and Gynaecologists

SFH Symphysis Fundal Height

SGA Small for Gestational Age

SMR02 Scottish Morbidity Record 02

WHO World Health Organization

## Introduction

Small for gestational age (SGA) babies are at increased risk of perinatal mortality<sup>1</sup>. Obstetric practice aims to identify these babies and deliver them at a time that minimises harm. It is assumed that improving detection of SGA will reduce the number of stillbirths, with some estimating a 20% reduction in mortality with optimal detection of SGA<sup>2</sup>. However, significant resources are required for SGA detection protocols, and instituting them may cause harm – through false positive diagnoses (causing unnecessary early delivery)<sup>3</sup>.

Ultrasound examination is commonly used for the detection of SGA, with fetal measurements recorded on fetal growth charts. In the UK and USA selective ultrasound screening is most often used, with referral for ultrasound based on maternal risk factors or symphysis-fundal height measurement. More recently, it was suggested that universal ultrasound is a more effective screening for the SGA fetus. Whilst a randomised controlled trial (RCT) showed that universal ultrasound tripled SGA detection in nulliparous women when compared with current selective screening, the potential to reduce perinatal mortality is less certain.

We conducted a retrospective population cohort study of all babies born SGA in Scotland in a 3-month period. The objective was to determine the potential to reduce perinatal mortality by improving antenatal detection of SGA babies. Specifically, we aimed to determine the current rate of antenatal SGA detection in Scotland; and to compare perinatal outcomes between SGA babies detected antenatally and those not detected (to identify the number of deaths that could, potentially, be prevented through SGA detection and early delivery).

## Methods

### Study design and setting

A retrospective population-based cohort study of babies born in the 15 consultant-led maternity units with >1000 deliveries in 2014 (including their alongside midwifery units) in Scotland between 1<sup>st</sup> December 2014 and 28<sup>th</sup> February 2015 inclusive (includes >98% Scottish Births<sup>4</sup>).

## Database

The cohort was identified from the Scottish Morbidity Record 02 (SMR02; the Maternity Inpatient and Day Case dataset) that is collated by the NHS National Services Scotland, Information Services Division (NHS ISD). SMR02 collects episode level data on all hospital deliveries in Scotland. The dataset includes patient identifiable information, maternal and baby characteristics and is estimated to be 99% complete across all health boards during the study period<sup>5</sup>. The missing data is due to a combination of home births (which are not recorded on SMR02 as there is no hospital admission) and missing data from maternity unit submissions. The National Records of Scotland is a civil registration system of all births in Scotland and was used to cross reference delivery numbers by the NHS ISD. There is a legal requirement to register all live births and all stillbirths (after 24 weeks gestation) within 21 days of birth.

## Ethics and anonymisation

As this was a quality improvement project formal ethical review was not required. Each individual maternity unit had a designated project lead who completed a "Confidential Data Release Request" that was approved by the Consultant Lead in each unit and the NHS National Services Caldicott Guardian. Data were de-identified in the delivering maternity unit and only anonymised data were returned centrally to the project coordinator.

## Population

The study population was women with singleton pregnancies delivering at 24 weeks gestation or more, in the 15 Consultant-Led NHS Maternity Units with >1000 deliveries in 2014 (including their alongside midwifery units) in Scotland between 1<sup>st</sup> December 2014 and 28<sup>th</sup> February 2015 inclusive.

The SGA cohort included all babies (live births and stillbirths) with a birth weight less than the 10<sup>th</sup> centile for their gestational age as defined by the appropriate sex-specific UK-WHO Child Growth Standards<sup>6</sup>, used for all Scottish children to define growth disturbance in childhood (as recorded in the Personal Child Health Record that every child receives). The WHO charts define optimal growth standards based on worldwide data of healthy children up to 4 years. These charts have been combined with birth data for gestations 23–42 weeks from the UK 1990 growth reference charts to produce the UK-WHO charts<sup>6</sup>. The 10<sup>th</sup> centile was chosen as this threshold is used as a definition in guidelines from WHO and countries including the UK, USA and Canada<sup>7</sup>.

A comparator "non-SGA group" was all singleton deliveries (live births and stillbirths) that were not identified as SGA (i.e. the SGA cohort) by the NHS ISD review of the SMR02 data set (see below). These deliveries were presumed to be at or above the 10<sup>th</sup> centile as defined by the UK-WHO Child Growth Standards<sup>6</sup>.

## Data extraction: outcomes, exposures and variables

**SGA cohort.** The SGA cohort was identified by NHS ISD and case details were forwarded to the project lead at each hospital, who performed detailed case note review. The SGA cohort included all live births identified as being less than the

10<sup>th</sup> centile for gestational age in SMR02. As the formula used by NHS ISD to calculate the birth weight centiles from the UK-WHO charts was only applied to live births, all stillbirths less than the 10th centile for 42 weeks gestational age (i.e. <3283g for boys and <3165g for girls) were identified to ensure that no cases were missed, with inclusion being clarified at the time of case note review.

A detailed case review of maternity and neonatal records of the cases was performed by each project lead using a standardised proforma (Extended data<sup>8</sup>). Birth weight centile was verified and additional variables (see below) were extracted from the hand-held maternity notes, hospital paper notes and/or the maternity paperless patient records systems that was in use in each unit. Data on APGAR scores were extracted from SMR02.

**Non-SGA cohort.** The non-SGA comparator group data was identified by the NHS ISD from the study population by excluding the cases that had been identified as SGA. A detailed hospital case note review was not performed for the non-SGA group. Instead NHS ISD extracted data from SMR02 on pre-specified variables to enable comparison between the SGA and non-SGA cohorts (see below).

## Outcomes and variables

**Outcomes.** The primary outcome was perinatal mortality in babies in whom SGA was not detected compared to those in whom SGA was detected. We used the definitions of perinatal mortality from the UK Perinatal Mortality Surveillance Report<sup>9</sup> (see Table 1). We have reported early neonatal death as this reflects obstetric events more closely than deaths up to 28 days.

Planned secondary outcomes were any admission to a neonatal unit of any level and APGAR score <7 at five minutes. These are both markers of perinatal morbidity.

**SGA cohort.** SGA detection was defined as documentation of SGA, fetal growth restriction or intrauterine growth restriction or small for dates in the case record prior to the onset of labour. Where it was not clear, or data were missing, it was presumed that SGA was not detected. The method of detection was defined as ultrasound diagnosed (ultrasound scan findings of an abdominal circumference or estimated fetal weight as <10th centile when measured on reference growth chart used by the local hospital at that time) or as clinically- suspected (determined by a reduced symphysis-fundal height measurement or

clinical palpation, according to local hospital protocol, without ultrasound confirmation).

Additional variables collected at case note review in the SGA cohort were maternal characteristics including age, body mass index (BMI) at booking and ethnicity. Baby characteristics included gestation at delivery (in days) and birth weight (in grams). Mode of delivery was classified as elective caesarean section (scheduled prior to the onset of labour), emergency caesarean section (unscheduled or performed during labour), operative vaginal delivery (forceps or ventouse) or spontaneous vaginal delivery.

Data regarding five clinical risk factors for SGA were also extracted including previously having a SGA baby (parous women), maternal age over 40 years at delivery, smoking over 10 cigarettes at the time of booking (data on any smoking in pregnancy was also collected for comparison with non-SGA cohort), hypertensive disorders in pregnancy (diagnosis of pre-existing hypertension, pregnancy induced hypertension and pre-eclampsia as per the individual unit's diagnostic criteria) and any attendance with reduced fetal movements. These are major risk factors in the Royal College of Obstetricians and Gynaecologists (RCOG)'s Green Top Guideline on SGA detection<sup>7</sup> that should trigger growth ultrasound screening and had high levels of completeness in antenatal records.

**Non-SGA comparator group.** Data extracted from SMR02 for the non-SGA comparator group included maternal characteristics (age, ethnicity, BMI at booking and smoking of any cigarettes during pregnancy) and baby details (gestation at delivery, birth outcome [live birth, stillbirth or neonatal death], admission to a neonatal unit, APGAR's <7 at 5 minutes).

**Growth ultrasound and biometry data.** For each pregnancy in the SGA cohort, the number of growth ultrasound scans performed was recorded. Growth ultrasounds were defined as those scans performed where the main intention was to obtain fetal biometry, from 22 weeks gestation onwards.

## Study size

Initial scoping of the SMR02 data suggested that the incidence of SGA babies less than 10th centile was approximately 5%, and we estimated an SGA detection rate of 25% based on local audit data (in line with published literature)<sup>10-12</sup>. We therefore estimated we would require a sample of 621 SGA babies to establish the SGA detection rate with 95% confidence level and absolute precision of 3%. Based on an annual delivery rate of approximately 56000 in Scotland<sup>13</sup>, we calculated a 3-month data collection would provide a study population of around 13000 and a study cohort of 650 SGA babies (allowing for 2% home births which are not recorded on SMR02 and missing data of ~5%).

## Data analysis

Data were de-identified at source, and anonymised data was collated and cleaned on a central database. Statistical analysis was performed using SPSS, version 22.0 and R studio, Version 1.1.453. Where data was normally distributed mean and standard

**Table 1. Perinatal mortality definitions.**

Outcome	Definition
Live Birth	Any baby born with signs of life <sup>9</sup>
Stillbirth	Any baby delivered at or after 24+0 weeks gestation, showing no signs of life, irrespective of when the death occurred <sup>9</sup>
Early Neonatal Death	Death of any live born infant (born after 20+0 weeks gestation) before 7 completed days after birth <sup>9</sup>
Perinatal Mortality	Stillbirth or Early Neonatal Death <sup>9</sup>

deviation were calculated. The t test was used to calculate p values. Where data was not normally distributed median and interquartile ranges were calculated. For data where proportions were calculated, Pearson's chi squared test (with Yates' correction) or Fisher's Exact Test (for numbers 10 or less) were used. Significance was defined as  $p < 0.05$ . 95% confidence intervals have also been reported. Logistic regression was performed to explore the influence of antenatal SGA detection on perinatal mortality and neonatal unit admission. Presence of one or more maternal risk factor for SGA (dichotomous variable), gestational age at delivery (continuous variable) and birthweight centile (continuous variable) were included in the model. Results are presented as unadjusted and adjusted odds ratio (OR and AOR; 95% confidence intervals, (CI)). Cases with missing fields were excluded from regression analysis.

To explore the effect of missing data on the cohort, we compared the SGA cohort with and without exclusion of sites with one or more missing data points in >15% cases (4 sites excluded; see supplementary Table S1 in extended data<sup>8</sup>).

Where there was missing data on antenatal SGA detection, SGA was presumed not to have been detected, and these cases were

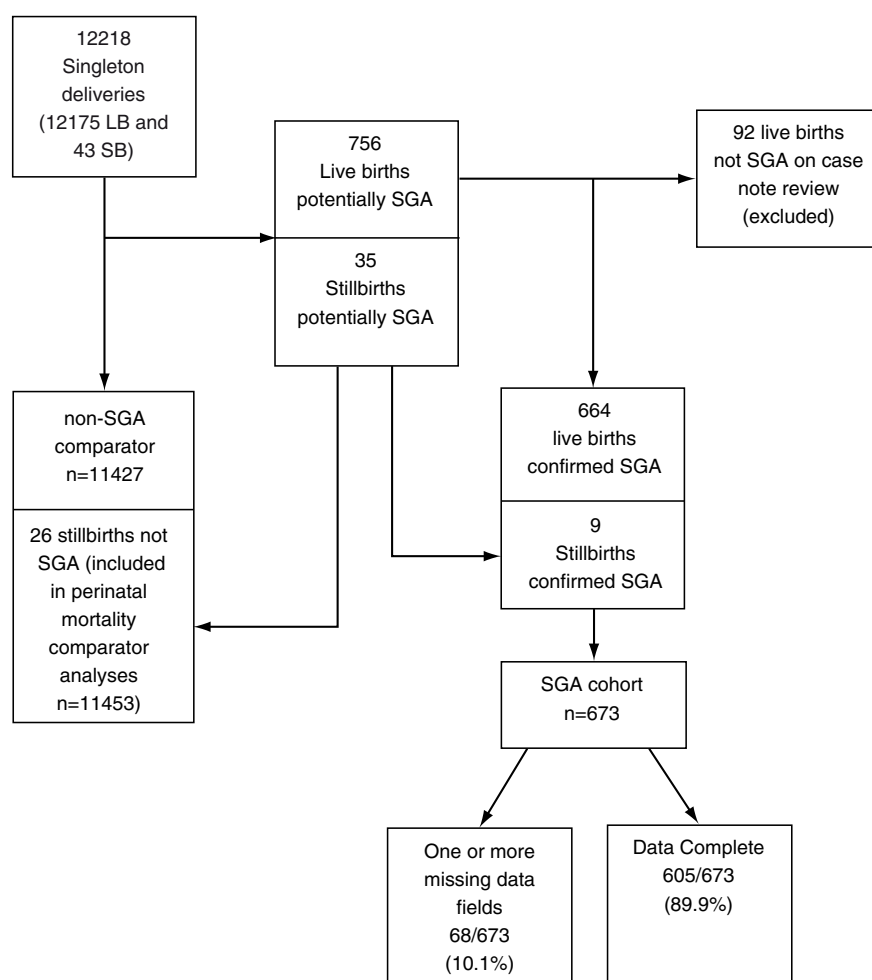
included in the denominator in analyses. The impact of including missing data on SGA detection in the denominator was explored using a sensitivity analysis excluding cases with missing data on SGA detection (25 cases excluded; see supplementary Table S2 in extended data<sup>8</sup>).

## Results

During the 3-month study period (1st December 2014 – 28th February 2015) there were 12619 births in Scotland, of which 12218 were singleton deliveries. There were 12175 singleton live births (with 25 [0.2%] neonatal deaths) and 43 stillbirths (0.35%). A flowchart is provided in Figure 1.

In total, 791 babies (756 live births and 35 stillbirths) were identified from the SMR02 as being potentially SGA. The remaining 11427 babies formed the non-SGA comparator group.

Following case note review 92 of 756 (12.2%) live births were re-classified as not SGA either due to discrepant birthweight or discrepant gestation. Due to anonymisation of data at source these babies could not be re-identified to include in the comparator group and were excluded from all subsequent analyses.



**Figure 1.** Flowchart of study population. SGA - small for gestational age, LB - livebirth, SB - stillbirth.



Of the 35 stillbirths with potential SGA (birth weights <10<sup>th</sup> centile for 42 weeks gestational age) 9 were found on case review to be <10<sup>th</sup> centile for gestation at delivery, and were included in the SGA cohort. The 25 stillbirths who were not SGA were included in the non-SGA comparator group for comparison of perinatal mortality rates (giving a total of 11453 babies for this comparison).

This gave a total cohort of 673 SGA babies, with an incidence of 5.5% (673/12218; 95% confidence interval [CI] 5.1, 5.9). Complete data was available for 623 cases (89.9%), with one or more field missing from 68 maternity records. The number of fields with missing data for each variable are included in [Table 2](#) and [Table 3](#). Four units had >15% of cases with at least one missing data field. A comparison was made between the full SGA cohort and the cohort with these units excluded. The two cohorts were similar (see supporting information S1 Table), thus all units were included in the analysis presented.

Of the 673 SGA babies, 183 were less than the 3<sup>rd</sup> centile (27.2% [95%CI 23.3, 31.3] of SGA babies; 1.5% [95% CI 1.1, 1.9] of singleton births); 144 between the 3<sup>rd</sup> and 5<sup>th</sup> centiles (21.4% [95% CI 17.5, 25.5] of SGA babies; 1.2% [95% CI 0.8, 1.6] of singleton births) and 346 were above the 5<sup>th</sup> centile (51.4% [95% CI 47.5, 55.6] of SGA babies; 2.9% [95% CI 2.5, 3.2] of Scottish Births).

### Participating units

All 15 consultant-led maternity units in Scotland with >1000 births/year contributed data.

### Comparison of SGA and non-SGA pregnancies

The details of the SGA and non-SGA cohorts are shown in [Table 2](#).

As expected, the SGA cohort was higher risk than the rest of the Scottish population, with more primiparous women (59.1% [398/673; 95% CI 55.3, 62.9] versus 43.0% [4918/11427; 95% CI 42.1, 44.0],  $p<0.0001$ ) and smokers (37.1% [250/673; 95% CI 33.6, 40.9] versus 16.4% [1870/11427; 95% CI 15.7, 17.1],  $p<0.0001$ ) in the SGA group compared to the non-SGA group.

The SGA cohort was statistically significantly slightly younger than the non-SGA group (29.1 years versus 29.6 years;  $p=0.015$ ) but this is unlikely to be of clinical significance. There was no difference in the proportion of women older than 40 years at delivery (2.7% [18/673; 95% CI 1.6, 4.2] versus 2.4% [270/11427; 95% CI 2.1, 2.7],  $p=0.7$ ), the mean gestation at delivery (39+1 weeks [95% CI 39+1, 39+2] versus 39+2 weeks [95% CI 39+1, 39+3],  $p=0.38$ ) or the Caesarean Section rate (32.4% [217/673; 95% CI 28.4, 36.3] versus 31.1% [3548/11427; 95% CI 30.2, 31.9],  $p=0.54$ ) between the two groups.

Ethnicity recorded was recorded as unknown more frequently in the non-SGA group (data from SMR02 routine data; 20.2% [2312/11427] unknown ethnicity) than in the SGA group (data obtained from hand searching of case notes; 2.8%

[19/673] ethnicity unknown;  $p<0.0001$ ). We therefore did not perform formal comparison of ethnicity as any differences are likely to reflect ascertainment bias.

Perinatal mortality was higher in the SGA group than in the non-SGA group (1.78% [12/673; 95% CI 0.9, 3.1] versus 0.44% [52/11451; 95% CI 0.4, 0.6],  $p=0.0002$ ) as was the stillbirth rate (1.34% [9/673; 95% CI 0.6 -2.3] versus 0.30 [34/11451; 95% CI 0.2, 0.4],  $p=0.0003$ ). The numbers of early neonatal death were small and no statistically significant differences were seen between the two cohorts (0.45% live births [3/664; 95% CI 0.1-1.3] versus 0.18% live births [20/11419; 95% CI 0.1, 0.3],  $p=0.13$ ). A higher proportion of SGA livebirths were admitted to the neonatal unit (14.3% [96/664; 95% CI 11.7, 17.1] versus 8.2% [939/11419; 95% CI 7.7, 8.8],  $p<0.0001$ ).

### Antenatal detection of SGA and comparison of outcomes in SGA detected versus SGA not detected groups

In 25 of the 673 SGA cases (3.9%) data was missing on whether SGA was detected antenatally. These cases were presumed not to have been detected antenatally in the subsequent analysis. 27.6% (186/673; 95% CI 24.3, 31.2) of SGA cases were identified prior to delivery (see [Table 3](#)). Of the 186 detected cases, 162 (87.1%) were diagnosed by ultrasound scanning, 23 (12.4%) were identified on clinical assessment (i.e. symphysis-fundal height measurements, not confirmed with ultrasound). In one case (0.54%) the method of detection was not documented. 454/673 women (67.5%; 95% CI 63.8%, 71.0%) who had an SGA baby had at least one growth ultrasound performed, with 322/673 (47.9%; 95% CI 44.0%, 51.7%) having more two or more growth scans performed in the pregnancy.

There was a higher proportion of mothers with one or more risk factors for SGA in the group with antenatal detection of SGA, than in the group where SGA was undetected (73.7% in SGA detection group [137/186; 95% CI 66.6, 79.7] vs 56.7% in SGA not detected group [276/487; 95%CI 52.1, 61.1],  $p<0.0001$ ) ([Table 3](#)). Babies in whom SGA was detected were born earlier (mean gestation at delivery 37+4 weeks [95% CI 37+2, 37+6] in SGA detected group vs 39+6 weeks [95% CI 39+5, 39+6] in the SGA not detected group [ $p<0.0001$ ]) and were lighter (mean birthweight centile 4.2 [95% CI 4.0, 4.4] vs 5.4 [95%CI 5.3, 5.5],  $p<0.0001$ ) than babies where growth restriction was not detected ([Table 3](#)).

The perinatal mortality was higher in the detection group compared to non-detected group (5.4% [10/186; 95% CI 2.8, 10.0] in the SGA detected group vs 0.4% [2/487 [95% CI 0.3, 2.2] in the non-detected group [ $p=0.0007$ ]) ([Table 3](#)). However, the increased odds of perinatal mortality did not remain statistically significant after adjusting for presence of maternal risk factors for SGA, gestation at delivery and birthweight centile (Unadjusted odds ratio [OR] of perinatal mortality in SGA detected group vs non-detected group 13.8 [95% CI 3.6, 90.2],  $p<0.0001$ ; Adjusted odds ratio [AOR] 2.4 [95% CI 0.4, 18.1],  $p=0.345$ ). Similarly, the unadjusted rate of neonatal unit admission was higher in the detection group (25.1% [45/179 livebirths; 95% CI 19.1, 32.3] vs 10.6% [51/483 livebirths;

**Table 2. Demographics of study population.** Small for gestational age (SGA) cohort vs non-SGA cohort. Statistical Tests

\*Pearson's Chi Square with Yates' Correction †Unpaired 2-sided t test ‡Fisher's Exact Test §denominator 664 livebirths

\*\*denominator 11453 total births ¶denominator 11421 live births.

Characteristic	SGA cohort (%) n=673	95% CI	Missing (%)	Non-SGA comparator (n=11427)	95% CI	Missing (%)	p
Maternal Demographic							
Primiparous (%)	398 (59.1)	55.3, 62.9		4918 (43.0)	42.1, 44.0	26 (0.2)	p<0.0001*
Maternal age at delivery (mean [sd] years)	29.1 (6.0)	28.8, 29.3	1 (0.2)	29.6 (5.7)	29.5, 29.7	0	p= 0.015†
BMI (mean [sd] kg/m <sup>2</sup> )	25.4 (5.5)	25.2, 25.7	3 (0.4)	26.2 (6.0)	26.1, 26.3	136 (1.2)	p=0.0004‡
Maternal age >40years at delivery (%)	18 (2.7)	1.6, 4.2	1 (0.2)	270 (2.4)	2.1, 2.7	0	p=0.7*
Any smoking (%)	250 (37.1)	33.6, 40.9	4 (0.6)	1870 (16.4)	15.7, 17.1	394 (3.5)	p<0.0001*
Ethnicity			19 (2.8)			2312 (20.2)	p<0.0001*
White British (%)	532 (78.2)	74.9, 81.2		7627 (66.8)	65.9, 67.6		-
White Non-British (%)	51 (7.5)	5.7, 9.8		377 (3.2)	2.9, 3.6		-
Asian (%)	52 (7.7)	5.8, 10.0		355 (3.1)	2.8, 3.5		-
African (%)	15 (2.2)	1.3, 3.7		127 (1.1)	0.9, 1.3		-
Other (%)	11 (1.6)	0.9, 3.0		629 (5.5)	5.1, 5.9		-
Delivery Details							
Gestation at delivery (mean weeks+days [sd days])	39+1(17)	39+1, 39+2	0	39+2 (28)	39+1, 39+3	39 (0.3%)	p=0.38†
Mode of Delivery			0			2 (0.02%)	
Vaginal birth (%)	365 (54.2)	50.4, 58.3		6459 (56.5)	55.6, 57.4		p= 0.26*
Operative Vaginal Delivery (%)	91 (13.5)	9.7, 17.5		1418 (12.4)	11.8, 13.0		p=0.43*
Caesarean Section (%)	217 (32.2)	28.4, 36.3		3548 (31.1)	30.2, 31.9		p=0.54*
Pregnancy Outcome							
Perinatal mortality (%)	12 (1.78)	0.9, 3.1		54 (0.47)	0.4, 0.6		p<0.0002‡
Stillbirth (%)	9 (1.34)	0.6, 2.3		34** (0.30)	0.2, 0.4		p<0.0005‡
Neonatal death (%)	3§ (0.45)	0.1, 1.3		20¶ (0.18)	0.1, 0.3		p=0.13‡
Neonatal unit admission (%)	96§ (14.3)	11.7, 17.1	19 (2.8)	939¶ (8.2)	7.7, 8.7	69 (0.6)	p<0.0001*

95% CI 8.0, 13.7; p<0.0001) but this relationship was not seen after adjusting for maternal risk factors, gestation and centile at delivery (OR of neonatal unit admission in SGA detected group vs non-detected group 2.6 [95% CI 1.7, 4.1], p<0.0001; Adjusted odds ratio [AOR] 0.85 [95% CI 0.5, 1.5], p=0.556).

Descriptions of the 12 perinatal death cases are given in supplementary material Table S3. Ten of the 12 perinatal deaths (83.3%) were identified as SGA antenatally. Six of these were extremely preterm (less than 28 weeks gestation) and/or extremely growth restricted (birthweight 500 grams or less).

Three (one neonatal death and two stillbirths) occurred at or more 36 weeks, despite being identified as being SGA.

Only two deaths were not detected as being SGA antenatally. One had growth scans performed, but SGA was not identified – and delivered at 41 weeks gestation. The other stillbirth with undetected SGA was a preterm stillbirth at 29 weeks gestation, with no preceding growth scans performed.

A sensitivity analysis was performed comparing the SGA detected cohort with the cohort where SGA was not detected antenatally, excluding the 25 cases with missing data on



**Table 3. Outcomes in small for gestational age (SGA) detected versus SGA not detected groups.**

Demographic/Outcome	SGA detected (n=186)	95% CI	Missing (%)	SGA not detected (n=487)	95% CI	Missing (%)	P
Maternal Demographic							
Primiparous	102 (54.8)	47.4, 62.1		296 (60.8)	56.3, 65.1		p= 0.189*
Maternal age at delivery (mean [sd] years)	29.1 (6.2)	28.7, 29.6	1 (0.5)	29.0 (5.9)	28.7, 29.3	0	p= 0.793†
BMI (mean [sd] kg/m <sup>2</sup> )	25.0 (5.5)	24.6, 25.4		25.6 (5.5)	25.3, 25.8		p= 0.184†
Ethnicity			5 (2.7)			14 (2.9)	p=1†
White (%)	165 (88.7)	83.1, 92.7		411 (84.4)	80.8, 87.4		p= 0.193*
Not white (%)	16 (8.6)	5.16, 13.83		62 (12.7)	10.0, 16.1		p= 0.173*
Risk Factors							
One or more risk factors (%)	137 (73.7)	66.6, 79.7		276 (56.7)	52.1, 61.1	11 (2.3)	p<0.0001*
Smoker >10 cigarettes per day (%)	65 (35.0)	28.2, 42.3	4 (2.2)	136 (27.9)	24.0 32.2	2 (0.4)	p=0.102*
Maternal age >40years at delivery (%)	5 (2.7)	1.0, 6.5	1 (0.5)	13 (2.7)	1.5, 4.6	0	p=1.0*
Previous SGA baby (%)	46 (24.7)	18.8, 31.7		64 (13.1)	10.3, 16.5	16 (3.3)	p=0.0004*
Hypertensive disorder (%)	21 (11.3)	7.3, 17.0	1 (0.5)	29 (6.0)	4.1, 8.5	22 (4.5)	p=0.028*
Reduced fetal movements (%)	65 (35.0)	28.2, 42.3	3 (1.6)	116 (23.8)	20.2 27.9	23 (4.7)	p= 0.005*
Pregnancy Outcome							
Gestation at delivery (mean weeks+days [sd days])	37+4 (23)	37+2, 37+6		39+6 (11)	39+5, 39+6		p<0.0001†
Birthweight centile [mean sd]	4.2 (2.8)	4.0, 4.4		5.4, (2.8)	5.3, 5.5		p<0.0001†
Perinatal mortality (%)	10 (5.4)	2.8, 10.0		2 (0.4)	0.26, 2.21		0.0001c
Stillbirth (%)	7 (3.8)	1.7, 7.9		2 (0.4)	0.07, 1.6		p=0.003‡
Neonatal death (%)	3§ (1.7)	0.4, 5.2		0**	0.0, 1.0		p=0.03*
Neonatal unit admission (%)	45§ (25.1)	19.1 32.3		51** (10.6)	8.0, 13.7	19 (3.9)	p<0.0001*

\*Pearson's Chi Square with Yates' Correction

†Unpaired 2-sided t test

‡Fisher's Exact Test

§denominator 179 live births

\*\*denominator 483 live births

antenatal SGA detection. Findings were similar to when these 25 cases were included in the SGA not detected group

## Discussion

We found that 5.5% of babies in Scotland were SGA at birth and perinatal mortality was higher in these babies compared to non-SGA babies, confirming that these babies are a high-risk obstetric population. The overall antenatal SGA detection rate in Scotland was 27.3%. This detection rate, although low, is consistent with other published studies<sup>10,12,13,15</sup>,

Overall, we found that the potential to decrease perinatal mortality by improving detection of SGA in our population was

much more limited than the 20% previously estimated<sup>2</sup>. Firstly, only one fifth of perinatal deaths occurred in SGA babies; thus, optimising SGA detection could not prevent the majority of perinatal deaths. Secondly, more than two thirds of SGA perinatal deaths were detected as being SGA antenatally, with only two of the SGA babies who died not recognised as being SGA antenatally. One of these was an antenatal stillbirth at 29 weeks gestation, when the risks of iatrogenic preterm delivery of SGA babies are significant and neonatal outcomes less certain. Only one stillbirth was at term (greater than 37 weeks gestation), when death could more certainly be considered preventable by early delivery. Growth ultrasound had been performed in this case, but SGA was not detected. Extrapolating from our data, we

calculate that even if all of SGA babies in singleton pregnancies were identified antenatally and identification could prevent 50% of perinatal mortality (which are both very optimistic estimates) then we could expect a maximal reduction in perinatal mortality of 0.5 per 1000 births, equating to around a 10% reduction in current perinatal mortality rates (5.1 per 1000[2]). In reality, SGA detection rates are only 60% even with universal screening for growth restriction[20], and there are very limited options for managing severely SGA babies. Thus, the potential for reducing mortality through improving detection of SGA is even more limited.

Our findings contrast to previously published UK data<sup>2</sup>, in our study perinatal outcomes were worse in babies where SGA was detected antenatally, compared to SGA babies who had not been recognised antenatally, with cases where SGA was recognised having higher rates of stillbirth, neonatal death and neonatal unit admission. Our findings likely reflect the fact that more severe SGA was more likely to be detected, with higher rates of maternal risk factors, and lower delivery gestations birthweight centiles in the detected group. When these factors were adjusted for, we found no persistent association between antenatal SGA detection and perinatal mortality or neonatal unit admission. These data need to be interpreted cautiously as the numbers are small, and the analysis is post hoc. Our results are consistent with the analysis of a French study where SGA pregnancies identified antenatally had worse neonatal outcomes than those SGA pregnancies not detected<sup>16</sup>. In addition, in the French study, those pregnancies which were wrongly identified as SGA (i.e. false positives) had worse outcomes than the true negative population (i.e. not SGA and correctly identified as that), highlighting the potential for iatrogenic harm in wrongly diagnosing SGA<sup>3,16</sup>.

### Strengths and limitations

Strengths of this study are that it is population based, with supplementary case note review to ensure data quality in the SGA cohort. We used the WHO 1990 birthweight centile charts for the diagnosis of SGA, which is clinically relevant as these are used for the diagnosis of growth disorders in Scottish children. We found 5.6% births less than the 10<sup>th</sup> centile, which is in line with other recent UK studies<sup>17</sup> and reflects the right shifting of birthweight centiles in high income countries over time.

Our study has several limitations. Firstly, SGA is a surrogate used to identify babies that are growth restricted. Some babies that do not reach their growth potential will have birthweights above the 10<sup>th</sup> centile (i.e. won't be SGA by our definition), and these would not be detected within our study. Secondly, stillborn babies lose weight *in utero* between death and delivery due to the process of maceration<sup>18</sup>, therefore the number of stillbirths associated with SGA are likely to be overestimated if (as in our study) unadjusted birthweights are used. This means the true perinatal mortality rate in SGA babies is likely to be lower than our findings suggest, and our estimates of the potential to reduce perinatal mortality through detection of SGA are overoptimistic. Thirdly, our focus was on detection of SGA and we did not collect data

on the management of pregnancies, which is likely to be an important factor in the perinatal outcomes of SGA babies. Fourthly, the comparator non-SGA group data was extracted from NHS ISD and not subject to case review thus comparisons between SGA and non-SGA babies may be at risk of ascertainment bias. Finally, we did not assess false positive rates i.e. those babies delivered due to a suspicion of SGA that subsequently were found to be of normal birthweight.

### Conclusions

Although avoiding any preventable perinatal death is extremely important, our findings suggest that focussing resources on improving detection of SGA alone is unlikely to have a major impact on perinatal mortality rates. To improve perinatal outcomes, we should focus on optimising high-quality care based on our current knowledge alongside commissioning high quality research into identifying better screening tools for the “at-risk” fetus.

### Data availability

#### Underlying data

The metadata for this study was provided by NHS ISD who are the data controllers. The Caldicott Guardian agreement by which we sourced the data does not allow for data sharing of the metadata as it is identifiable at a patient and a practitioner level. Any suitably qualified researcher with the appropriate approval would be able to obtain this data directly from NHS ISD. Researchers would need to complete a “[Confidential Data Release Form](#)” available from NHS National Services Scotland to gain approval. They can then use our study proforma to request the required data from NHS ISD (see extended data).

#### Extended data

Open Science Framework: An evaluation of the potential to improve perinatal outcomes by improving antenatal detection of small for gestational age babies in Scotland: a retrospective population cohort study. <https://doi.org/10.17605/OSF.IO/EWTMB><sup>8</sup>

This project contains the following extended data:

- Study Proforma.xls (Proforma used for data extraction)
- Supporting info.pdf (PDF containing Supplementary Tables 1–3)

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

### Acknowledgements

Data collection and case note review performed by : Alan Baird, Mairead Black, Jandy Fernandes, Emily Frier, Hilary Godsmann, Naomi Griffiths, Rachael Hall, Lucy Harrington, Chaitra Hirae, Ruth Howie, Claire McCormack, Sarah Miliken, Nada Mufti, Vicki Thompson, Alexandra Viner. We are grateful for advice and feedback provided by the Scottish Government Stillbirth Subgroup.

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# Open Peer Review

Current Peer Review Status: ? ?

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## Version 1

Reviewer Report 03 August 2020

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Ashish KC

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Abstract

**Method** - Please mention the data analysis strategy in the research.

**Result** - Provide the total singleton birth engaged. Instead of using 5.5% followed with number, use XX% (95%, XX-XX). There is confusion in presenting the data that "there was no difference in perinatal mortality whether SGA was detected or not..." as it presents 5.4% (95% CI, 2.8-10.0) vs 0.4% (95% CI, 0.3-2.2). This data shows difference in two group without adjustment. I think after adjusting to risk factors the risk might have changed, so either present the adjusted risk or rather not present it. It is confusing.

**Conclusion** - The authors present "Despite only around a quarter of SGA being identified antenatally, ..." This data has not been presented in the result of abstract, either present it or remove it from the abstract conclusion.

Main text

**Introduction** - A couple of sentences on the national and global burden of SGA and death attributed to it will provide the importance of the study.

**Method** - My main concern is the timing of detection of SGA during antenatal period. The timing of detection of SGA during antenatal period corresponds with the preventive measures used for managing the pregnancy and birth. The author needs to describe it well. Can the authors also distinguish between antenatal and intrapartum stillbirth? This is a key value, as the timing of death associated with timing of detection of SGA provides the quality of antenatal and intrapartum care.

**Results**

The flow diagram is confusing. A STROBE flow diagram for cohort design needs to be redone.

Table 3 also needs to provide the categorization of antepartum and intrapartum stillbirth. Also,

the timing of detection of SGA antenatally with the number of perinatal death is important, either a graph on this or a separate supplementary table will be interesting.

### Discussion

One other key factor is infection during pregnancy not been captured by the registry, this needs to be mentioned in the limitation section.

**Is the work clearly and accurately presented and does it cite the current literature?**

Yes

**Is the study design appropriate and is the work technically sound?**

Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**

Partly

**If applicable, is the statistical analysis and its interpretation appropriate?**

Yes

**Are all the source data underlying the results available to ensure full reproducibility?**

Partly

**Are the conclusions drawn adequately supported by the results?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Perinatal epidemiology.

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Reviewer Report 20 March 2020

<https://doi.org/10.21956/wellcomeopenres.17002.r38085>

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**Sophie Relph** 

Department of Women and Children's Health, School of Life Course Sciences, Faculty of Life Sciences and Medicine, King's College London, London, UK

It was a pleasure to review this important piece of work; it is timely and a key contribution to



health policy on antenatal screening methods.

The research sets out to determine whether there is scope for improving the rate of antenatal detection of the small for gestational age (SGA) fetus and, if so, whether this is likely to impact significantly on perinatal mortality. This was a population-based cohort study in Scotland. The article concludes that during the 3-month study period, antenatal detection of Scottish SGA was similar to that in published reports from other national settings, but that only a small proportion of perinatal mortality occurred in babies who were also SGA. In the vast majority of these, SGA had been antenatally detected anyway, so it was concluded that there was little room for improving national perinatal death rates through improved antenatal detection of SGA.

The article is well-written with only a small number of typographical errors. It could therefore benefit from an additional proofread. The text is easy to understand.

My key comments are targeted to areas in which I think the article could be improved:

1. The number of perinatal deaths in SGA babies (n=12) is too small to make a conclusion about the potential to improve rates of perinatal death by increasing SGA detection. It is unclear in the text why the population cohort was limited to 3 months of births. I realise that the burden of reviewing maternity records for 791 babies is high, and less biased than only reviewing the rate of SGA detection in records for babies with perinatal deaths. However, given the primary aim of the study was to assess the potential of improving SGA detection for babies who die in the perinatal period, data collection on SGA detection in a larger cohort of SGA deaths would be more informative. I suggest you: (a) provide reasons for the limited time frame (b) indicate why you chose the strategy of assessing SGA detection in all babies rather than targeted in perinatal deaths and (c) suggest future work to cover the latter.
2. On this same point, the aim of the study and the primary outcome is 'perinatal mortality in babies in whom SGA was not detected compared to those in whom SGA was detected', however the statistical power of the study was calculated on the rate of SGA detection in the whole population. Where the power calculation is not targeted to the primary outcome, this needs to be explained. I expect this was the decision because it was not expected to be possible for the study to be powered adequately for the primary outcome. The text should therefore be explicit about this and it should be described as a key limitation in the discussion.
3. As someone who is familiar with birth weight percentile charts, I was still a bit confused about the interchangeable use of the terms UK1990, UK-WHO, WHO-1999 and WHO birth weight charts. In particular, the second paragraph under 'Population' subsection of methods cites two types of chart but uses the same reference for both. Please check and be consistent with the terms.
4. There is quite a bit of repetition between the 'Population' and 'Data extraction' subsections of Methods. Please review and consider cutting.
5. In 'outcomes and variables' you cite the key risk factors for SGA on which you collected data. You refer to the RCOG SGA guidance as rationalisation for this. However, RCOG guidance only defines 'severe PIH' (not all PIH) as a risk factor and doesn't cite reduced fetal

movements as a risk factor in its screening algorithm. Please consider rephrasing this and justify why these factors (all PIH/reduced FM) have been included.

6. In describing your choice of risk factors for SGA you also comment that choice was based on 'high level of completeness'. I wonder whether you mean 'high prevalence' and whether this is the reason that you haven't included other co-morbidities such as CKD/diabetes, which both are major risk factors for SGA, but are present less commonly.
7. Please note, I couldn't work out how to view the supplementary tables and so have not reviewed these.
8. In the second paragraph of 'Data Analysis' you have referenced paper 8, but I think this may be an error.
9. Figure 1 doesn't include the neonatal deaths – this confused me at first because there are only 9 stillbirths reported but the abstract reported that you had 12 perinatal deaths. It might be nice to add a box for neonatal deaths that were SGA/not.
10. It would be nice to know how you determined that data on reduced fetal movements/PIH/PET or hypertension was missing, rather than just not a problem. In my experience, absence of a diagnosis is not the same as missing information – but perhaps SMR specifically codes absent diagnoses?
11. In the paragraph just above the subsection on 'Participating Units' you list 2 of the denominators as 'singleton births' but the other as 'Scottish births'. Presumably the latter includes multiple births and is not the same thing. Please check.
12. In Table 3 – I think there is a typo for the p value of perinatal mortality.
13. I am a bit uncertain about the adjustments made for the perinatal mortality model. You have concluded that there is no difference in perinatal mortality between detected and undetected SGA after adjusting for birthweight and gestational age (although there was without adjusting), which are outcomes as a result of SGA detection as well as potentially predictors in the case of perinatal mortality from severe SGA. The difference in this small number of deaths is likely be due to detection of severe SGA vs non-detection of borderline SGA. The relationship is quite complex and I can't quite work out whether the approach is right – have you taken statistical advice on this?
14. I am a little concerned regarding the case details shared in the penultimate paragraph. I think that women could be identified here – they are the only women with these specific characteristics in the whole of Scotland. Is this an information governance issue or do you have individual consent for case reporting?

To summarise, I think that most of this can be resolved quickly – but I would recommend more explanation and justification for decisions made in the paper.

**Is the work clearly and accurately presented and does it cite the current literature?**

Yes

**Is the study design appropriate and is the work technically sound?**

Partly

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

Partly

**Are all the source data underlying the results available to ensure full reproducibility?**

Yes

**Are the conclusions drawn adequately supported by the results?**

Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Clinical expertise with an academic interest in perinatal epidemiology, fetal growth and stillbirth.

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

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